

Absence of 185delAG mutation of the *BRCA1* gene and 6174delT mutation of the *BRCA2* gene in Ashkenazi Jewish men with prostate cancer

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Summary Epidemiological studies have demonstrated a clustering of breast and prostate cancers in some families. Moreover, there is an increase in the number of cases of prostate cancer in families with inherited mutations of the breast cancer susceptibility gene *BRCA1*. We assessed the role of *BRCA1* and *BRCA2* in prostate cancer. We tested for the *BRCA1* 185delAG frameshift mutation, found in 0.9% of Ashkenazi Jews, and the *BRCA2* 6174delT mutation, found in 1% of Ashkenazi Jews, in Ashkenazi Jewish men with prostate cancer. We studied 60 Ashkenazi men with prostate cancer. A family history was obtained by interview or a self-report questionnaire. Histological confirmation of diagnosis was obtained for all subjects. Ethnic background was confirmed for all subjects by self-report or interview. Mutations of *BRCA1* and *BRCA2* were detected by amplification of lymphocyte DNA from peripheral blood according to standard polymerase chain reaction (PCR) and dot blot procedures. Patients' ages ranged from 55 to 80 years (mean \pm s.d. 70 ± 5.25). There were six men with a family history of prostate cancer; three of these had a father with prostate cancer. Five of the men had a family history of breast cancer, in a mother, a sister or an aunt. None of the men had a family history of both breast and prostate cancer. None of the 60 men carried the 185delAG *BRCA1* or 6174delT *BRCA2* mutations. Of 268 Ashkenazi Jewish women with sporadic breast cancer, tested in an unrelated study, 16 carried either the 185delAG mutation of *BRCA1* or the 6174delT mutation of *BRCA2*. There was a significant difference in the incidence of the *BRCA1* and *BRCA2* mutations in the breast and prostate cancer cases ($P = 0.05$, two-tailed Fisher's exact test). The contribution of germline *BRCA1* and *BRCA2* mutations to prostate cancer incidence is probably small and could be limited to specific subgroups.

Keywords: *BRCA1*; *BRCA2*; prostate cancer; Jewish mutations

Prostate cancer is the most common malignancy found in American men (Boring et al, 1994). Although dietary fat plays a role in the development of this cancer (Pienta and Esper, 1993), and possibly also vasectomy (Giovannucci et al, 1993), family history is one of the strongest risk factors (Whittemore et al, 1995). Indeed, there may be a gene for prostate cancer on the long arm of chromosome 1 (Smith et al, 1997) although there is some evidence that the breast cancer susceptibility genes *BRCA1* and *BRCA2* may also be involved.

Epidemiological studies have demonstrated a clustering of breast and prostate cancers in some families (Sellers et al, 1994). Moreover, there is an increase in the number of cases of prostate cancer in families with inherited mutations of *BRCA1* (Ford et al, 1994; Struwing et al, 1997); loss of heterozygosity studies also implicate *BRCA1* (Gao et al, 1995 *a* and *b*), which is located on the long arm of chromosome 17.

To assess the role of *BRCA1* in prostate cancer, Langston et al (1996a) screened for germline *BRCA1* mutations in a subset of men from an ongoing population-based case-control study of prostate cancer. Langston et al selected a group of 49 men with prostate cancer in whom genetic factors were most likely to be

relevant, and found *BRCA1* mutations in seven (14.3%) of these men: one known *BRCA1* mutation plus six more rare sequence variants. One mutation that Langston et al found was in a Jewish family with multiple cases of prostate cancer and the mutation was 185delAG.

Since *BRCA1* and *BRCA2* were cloned, many unique mutations of these two genes have been detected in the germ line of individuals with breast and ovarian cancer (Miki et al, 1994; Wooster et al 1994; Friedman et al, 1995). In high-risk pedigrees, female carriers of *BRCA1* mutations have an 80–90% lifetime risk of breast cancer and a 40–50% lifetime risk of ovarian cancer (Ford et al 1994). Following the finding of a 185delAG frameshift mutation of *BRCA1* in several Ashkenazi Jewish breast/ovarian cancer families, the frequency of this mutation was found to be 0.9% (Struwing et al, 1995). The 6174delT mutation of *BRCA2* has a 1% incidence in Ashkenazi Jews (Oddoux et al, 1996). We studied a group of Ashkenazi men with prostate cancer, but failed to find the 185delAG or 6174delT mutations.

SUBJECTS AND METHODS

Participants for our study were found via urology and radiation oncology clinics, and all eligible patients were asked to take part in the study. A family history was obtained by interview or self-report questionnaire. Histological confirmation of diagnosis was obtained for all subjects. Ethnic background was confirmed for all subjects by self-report or interview. All participants gave informed consent for genetic studies and were not given the option to know

Received 23 October 1997

Revised 14 January 1998

Accepted 30 January 1998

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their test results. Extensive genetic counselling, covering options for detection and prevention, was available. Although we used mostly sporadic cases of prostate cancer, some germline mutations would still be expected. Indeed, Langston et al (1996b) found *BRCA1* germline mutations in 10% of a cohort of young women with breast cancer, many without a family history of breast or ovarian cancer. Fitzgerald et al (1996) also noted that these mutations can be present in young women with breast cancer who do not belong to families with multiple affected members.

Mutations of *BRCA1* and *BRCA2* were detected by amplification of lymphocyte DNA from peripheral blood according to standard polymerase chain reaction (PCR) and dot blot procedures (Sambrook et al, 1989). The following primers for PCR were added to the reaction mixture:

BRCA1 primers

5' > GAA GTT GTC ATT TTA TAA ACC TTT < 3' (forward)

5' > TGT CTT TTC TTC CCT AGT ATG T < 3' (reverse)

BRCA2 primers

5' > AGT TTC TAA AAT ATC ACC TTG TG < 3' (forward)

5' > GTC TGA ATG TTC GTT ACT TTT AA < 5' (reverse)

Aliquots of amplified DNA were transferred to membranes (Hybond) using a standard protocol (Sambrook et al, 1989). Hybridization was performed for 60 min at 42°C. The following ³²P-labelled probes were used for dot blot analysis:

BRCA1

5' > AAT CTT AGA GTG TCC CA 3' < (wild type)

5' > ATC TTA GTG TCC CAT CT 3' < (185delAG mutant)

BRCA2

5' > ACA GCA AGT GGA AAA TC 3' < (wild type)

5' > ACA GCA AGG GAA AAT CT 3' < (6174delT mutant)

Positive and negative controls were included in all runs.

RESULTS

We studied 60 Ashkenazi men with prostate cancer, ranging in age from 55 to 80 years (mean \pm s.d. 70 ± 5.25). There were six men with a family history of prostate cancer, three of whom had a father with prostate cancer. Five of the men had a family history of breast cancer, in a mother, a sister or an aunt. None of the men had a family history of both breast and prostate cancer. None of the 60 men carried the 185delAG *BRCA1* or 6174delT *BRCA2* mutations.

Our results in prostate cancer may be compared with our results in breast cancer. Of 268 Ashkenazi Jewish women with sporadic breast cancer previously tested in an unrelated study, 16 carried either the 185delAG mutation of *BRCA1* or the 6174delT mutation of *BRCA2* (Dr C. Eng, personal communication). There was a significant difference in the incidence of the *BRCA1* and *BRCA2* mutations in the breast and prostate cancer cases ($P = 0.05$, two tailed Fisher's exact test).

CONCLUSIONS

A recent epidemiological analysis by Isaacs et al (1995) failed to identify a significantly increased risk of breast cancer among relatives of prostate cancer patients. Our findings are consistent with the findings of Isaacs et al. Furthermore, there is no evidence of genetic linkage between *BRCA1* and prostate cancer in high risk families (Eastman, 1996; Stephenson, 1996).

The results of our study pertain only to the 185delAG mutation of *BRCA1* and the 6174delT mutation of *BRCA2*. Nevertheless, the overall contribution of germline *BRCA1* and *BRCA2* mutations to prostate cancer incidence are probably small and could be limited to specific subgroups, such as that studied by Langston et al (1996a). Indeed, a mutation of a tumour-suppressor gene distal to the *BRCA1* locus on the long arm of chromosome 17 may make a much greater contribution (Williams et al, 1996). A mutation on chromosome 1 may also play a role (Smith et al, 1997). Larger population-based studies of tumour and normal tissue from men with prostate cancer would be worthwhile as well as a complete analysis of *BRCA1* and *BRCA2* in the subjects.

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